Notes on the design of bioequivalence study: Amodiaquine

Notes on the design of bioequivalence studies with products invited to be submitted to the WHO Prequalification Team – Medicines (PQTm) are issued to aid manufacturers with the development of their product dossier. Deviations from the approach suggested below can be considered acceptable if justified by sound scientific evidence.


Below, additional specific guidance is provided on the invited immediate release products containing amodiaquine.

Pharmacokinetics of amodiaquine
Amodiaquine is quickly absorbed and biotransformed into its main active form, desethylamodiaquine. The median amodiaquine $T_{max}$ value is 0.91 h.

Amodiaquine is eliminated principally through biotransformation with only around 2% excreted unchanged in urine. Its half-life is 24-28 hours.

When amodiaquine was taken with a high fat meal in healthy volunteers, the $C_{max}$ and $AUC_{0-t}$ of amodiaquine increased 23% and 58%, respectively, compared to that observed under fasting conditions. The $C_{max}$ and $AUC_{0-t}$ of the active metabolite desethylamodiaquine increased 18% and 12%, respectively, with a high-fat meal, compared to that observed under fasting conditions.

Guidance for the design of bioequivalence studies:
Taking into account the pharmacokinetic properties of amodiaquine, the following guidance with regard to the study design should be taken into account:

**Design:** A cross-over design is recommended.

**Dose:** As the EoI includes amodiaquine 75 mg and 150 mg (or 76.5 mg and 153 mg) tablets co-blistered with sulfadoxine/pyrimethamine tablets, the 150 mg (or 153 mg) strength should be tested.

**Fasting/fed:** The bioequivalence study can be conducted in the fasted state as although it is generally taken after meals, this seems to be related to tolerability and not pharmacokinetics.

**Subjects:** Healthy adult subjects should be included in the bioequivalence study. It is not necessary to include patients.

**Sample size:** Amodiaquine values for intra-subject %CV have been reported to range between 25%-37% for $C_{max}$ and 15%-30% for AUC. These data may facilitate the calculation of a sufficient sample size for the bioequivalence study.
**Washout:** Taking into account the elimination half-life of amodiaquine of 28 h, a wash out period of 2 weeks is recommended.

**Blood sampling:** The blood sampling should be intensive in the first 2 hours since median $T_{max}$ occurs before 1 hour. It is not necessary to take samples after 72 hours. For example, blood samples might be taken at pre-dose, and at 00.17, 00.25, 00.33, 00.50, 00.67, 00.83, 01.00, 01.25, 01.50, 01.75, 02.00, 02.50, 03.00, 03.50, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 24.00, 48.00 and 72.00 hours after drug administration.

**Analytical considerations:** Information currently available indicates that it is possible to measure amodiaquine in human plasma using LC-MS/MS analytical methodology. The bioanalytical method should be sufficiently sensitive to detect concentrations that are 5% of the $C_{max}$ in most profiles of each formulation (test or comparator).

**Parent or metabolite data for assessment of bioequivalence:** The parent drug is considered to best reflect the biopharmaceutical quality of the product. The data for the parent compound should be used to assess bioequivalence of amodiaquine.

**Statistical considerations:** The data for amodiaquine should meet the following bioequivalence standards in a single-dose cross-over design study:

- The 90% confidence interval of the relative mean $AUC_{0-72h}$ of the test to reference product should be within 80-125%.

- The 90% confidence interval of the relative mean $C_{max}$ of the test to reference product should be within 80-125%.

Information currently available to PQTm suggests that the comparator product is a highly variable drug product for $C_{max}$ in the fasted state. Widening of the acceptance range for $AUC_{0-t}$ is not acceptable, but the applicant may design a replicate cross-over study to estimate variability more accurately and to widen the acceptance range for $C_{max}$. For more information on replicate study designs and average scaled bioequivalence, refer to Section 7.9.3 of Annex 7, TRS 992.